

REMARKS

The invention relates to the discovery of a novel antibody which inhibits entry of HIV into cells and which specifically binds to a cellular chemokine receptor protein.

Claims 1-2 and 4-10 are pending in the application. Claim 3 was previously canceled, without prejudice, in Paper No. 12, which was filed in response to the Office Action mailed May 22, 1998 (Paper No. 11). The subject matter contained in canceled claim 3 was incorporated into amended claim 1. Claims 11-24 were withdrawn previously as being drawn to a non-elected invention.

Claim 1 has been amended to delete the term "anti-immunodeficiency virus" as it refers to an antibody. Since the antibody is disclosed as an antibody throughout the specification, no new matter has been added by way of this amendment. In addition, claim 1 has been amended to recite a "cellular" chemokine receptor protein. Support for this amendment is found throughout the specification and in the examples, wherein two cellular chemokine receptor proteins, CXCR4 and CCR5, are exemplified. Thus, this amendment does not constitute new matter.

Claims 4, and 5 have been amended to depend from claim 1 instead of canceled claim 3. Claims 4 and 5 have also been amended to more particularly point out that which Applicant regards as his invention. No new matter has been added by way of these amendments.

Applicant acknowledges that the present invention has been accorded the benefit of the earlier filing date of application Serial No. 60/020,396, of June 25, 1996.

Rejection of Claims 1-2 and 4-10 Under 35 U.S.C. § 112, Second Paragraph

Claims 1-2 and 4-10 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. More specifically, the Examiner has maintained his rejection, as previously set forth in Paper No. 11, that claim 1, from which the remaining claims depend, is indefinite in that it is drawn to an "anti-immunodeficiency virus antibody" which term is "unclear as to whether the antibody is directed to a viral protein or to a chemokine receptor on a cell." The Examiner suggests that the term be deleted from claim 1. Applicant has complied with the Examiner's suggestion and have deleted the term from claim 1.

The Examiner further contends the term "HIV receptor protein" of claim 4 is also vague since it is "unclear whether the antibody is directed to a viral receptor such as gp160 or a cellular receptor such as CD4 which binds to HIV." Claim 4 has been amended to recite that the antibody is directed to a cellular protein. No new matter has been added by way of this amendment since it is clear from the disclosure in the specification that examples of proteins to which the antibody binds include CXCR4 and CCR5, both being cellular proteins.

Additionally, the Examiner contends that claim 5 is vague and indefinite in the recitation of "cellular cofactor for a cellular HIV receptor" since, in the Examiner's view, the term is unclear as to whether the cofactor activity is actually intended to be directed to another cellular receptor such as CD4 or to a cofactor activity for HIV infection. Claim 5 has been amended to recite that the protein is a cellular cofactor for a cellular protein which is an HIV receptor protein. Since the meaning of this term is clearly defined in the specification (page 10, lines 23-24): "A 'cellular co-factor' as used herein, is defined as a protein which is required, in association with a cellular receptor for HIV, for entry of HIV into cells." The specification goes on to state that a protein may be both a cellular co-factor and an HIV-receptor protein in its own right. Hence the need for both claim 4 and claim 5. Indeed, the antibody of the invention binds to a cell protein, CXCR4 (also known as "fusin") which is both a cellular co-factor and an HIV-receptor protein depending on the cell type to be infected (specification at page 10, lines 25-29). The term is neither vague nor indefinite because it is amply defined in the specification.

As pointed out previously herein, the claims are to be read in the light of the specification. Further, under the patent law, the applicant is his own lexicographer. Therefore, where, as here, Applicant has clearly defined "cellular cofactor for a cellular HIV receptor" in the specification, claim 5 cannot be vague under 35 U.S.C. § 112, second paragraph, because it recites the term.

The Examiner further contends that claim 8 is vague and indefinite because it is unclear what would constitute a "synthetic antibody." This is because, in the Examiner's opinion, even a monoclonal antibody can be considered a "synthetic antibody." Applicant respectfully submits that the term "synthetic antibody" is not vague or indefinite and that claim 8 reciting the term is not vague under 35 U.S.C. §112, second paragraph.

The term "synthetic antibody" is defined in the specification (page 16, lines 7-14) which states, in part:

By the term "synthetic antibody" as used herein, is meant an antibody which is generated using recombinant DNA technology, such as, for example, an antibody expressed by a bacteriophage as described herein. The term should also be construed to mean an antibody which has been generated by the synthesis of a DNA molecule encoding the antibody and which DNA molecule expresses an antibody protein, or an amino acid sequence specifying the antibody, wherein the DNA or amino acid sequence has been obtained using synthetic DNA or amino acid sequence technology which is available and well known in the art.

Thus, the specification makes clear that a "synthetic antibody" must be required by recombinant DNA methodologies and does not encompass monoclonal antibodies produced by hybridoma technology. Indeed, the specification (at page 16, lines 4-7) distinguishes between monoclonal antibodies and synthetic antibodies produced by recombinant DNA techniques such as expression of the DNA encoding the antibody molecule in a bacteriophage expression system: "Thus, in contrast to conventional monoclonal antibody synthesis, this procedure immortalizes DNA encoding human immunoglobulin rather than cells which express human immunoglobulin." Further, this is an important distinction in that the invention also encompasses expression of the DNA encoding the antibody of the invention, or portions thereof, in otherwise susceptible cells to render the cells resistant to HIV infection (specification at page 16, lines 20-28).

Therefore, the term "synthetic antibody" is clearly defined in the specification and does not, as urged by the Examiner, include conventional monoclonal antibodies. Thus, when read in light of the disclosure of the specification, as required pursuant to the current patent law, claim 8 is not vague or indefinite, and the rejection of the claim on this basis under 35 U.S.C. § 112, second paragraph, should be reconsidered and withdrawn.

The Examiner also contends that claims 4-7 are indefinite in that they depend from previously-canceled claim 3. The claims have been amended to correct the respective dependencies.

Rejection of Claims 1-9 Under 35 U.S.C. § 112, First Paragraph

Claims 1-9 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. More specifically, the Examiner contends that the specification only sets forth the 12G5 monoclonal antibody which appears specific for the CXCR4 chemokine receptor (fusin). The Examiner further contends that the specification does not enable antibodies to other chemokine receptors nor antibodies which would inhibit non-T-cell tropic strains of HIV.

In addition, relying on his previous arguments that an "anti-immunodeficiency virus antibody" must, according to the Examiner's view of the art accepted terminology, bind to a viral protein and cannot, by definition, bind to a cell protein, the Examiner contends that the specification does not enable an antibody specific for an immunodeficiency virus at all. The Examiner therefore concludes that the specification does not enable the production of "anti-immunodeficiency virus antibodies," anti-chemokine receptor antibodies able to bind to any cellular protein, or even any chemokine receptor with a reasonable expectation of success and without undue experimentation.

Applicant respectfully traverses this rejection. Preliminarily, Applicant does not claim "anti-immunodeficiency virus antibodies" which bind to any cellular protein and inhibit immunodeficiency virus. Rather, amended claim 1 recites an antibody which binds to a chemokine receptor protein essential for immunodeficiency virus entry into a cell wherein the chemokine receptor protein is a cellular protein which is not CD4. Therefore, the claim recites an antibody directed against specific cell proteins not to any cell protein as urged by the Examiner. Further, the Examiner acknowledges that "HIV and SIV appear to utilize a very limited number of coreceptors for infecting cells." (Office Action, Paper No. 12, at page 4, lines 22-24). Thus, the number of proteins to which the claimed antibodies will bind are a limited few. Although Applicant has produced antibodies to one of those few proteins which are within the scope of the claims, the Examiner contends that the specification does not enable the claims commensurate with their scope.

Applicant respectfully submits that undue experimentation would not be required to arrive at the present claims where only a limited number of cellular proteins exist and where antibodies to one such protein which inhibits virus infection has been reduced to practice. It is

well-settled that the disclosure need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908 (C.C.P.A. 1970). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. MPEP § 2164.01. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *Id.* (citing *In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A. 1976)). Further, the specification need not disclose what is well known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. MPEP § 2164.05(a) (citing *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991)). Therefore, under current law, enablement does not require a working example and experimentation is allowed so long as it is not undue.

In addition, it is hornbook law that "representative samples are not required by the statute and are not an end in themselves." *In re Robins*, 429 F.2d 452, 456-57, 166 USPQ 552, 555 (CCPA 1970). Thus, generic claims are not precluded by 35 U.S.C. § 112, first paragraph, and enablement does not require working examples for each species encompassed by a claim. However, notwithstanding the above, in the present application, Applicant has in fact produced an antibody, 12G5, which binds a chemokine receptor protein other than CD4 and inhibits immunodeficiency virus infection of cells.

Given the present state of the prevailing law regarding enablement wherein not even one working example is required, the present invention, which has in fact been reduced to practice in the disclosure of the specification and which sets forth a working example, is certainly enabled under 35 U.S.C. § 112, first paragraph. The specification sets forth numerous assays for determining the anti-immunodeficiency virus activity of the antibodies of the invention. Thus, following the guidance of the disclosure of the specification, a person of ordinary skill in the art could, without undue experimentation, by engaging in experimentation typically engaged in by the art, be able to practice the invention within the scope of the claims and produce anti-immunodeficiency virus antibodies which bind a chemokine receptor protein (not CD4) and inhibit virus infection, just as Applicant has done in reducing his invention to practice.

Contrary to Examiner's arguments, Applicant has produced an antibody which binds to a cellular protein and inhibits HIV infection. Therefore, the Examiner's argument that Applicant has not enabled an "anti-immunodeficiency virus antibody" at all because the antibody of Applicant's invention binds a cell protein and not a virus protein is untenable and should be withdrawn. Thus, the specification does enable an anti-immunodeficiency virus antibody as defined in the specification.

The Examiner states that the specification on page 31, lines 1-15, provides evidence that antibodies other than 12G5 are not enabled. Applicant strenuously disagrees. The point being made on page 31 of the specification is that 12G5 is not specific for each and every chemokine receptor protein. This is not surprising and with all due respect, the Examiner's reasoning is flawed. Applicant's claim 1 does not recite that 12G5 binds to all chemokine receptor proteins. Rather, Applicant's claim 1 claims an antibody which, like 12G5, binds a chemokine receptor protein and inhibits entry of HIV into a cell. Applicant's claimed antibody is exemplified by 12G5. Other antibodies having the property of 12G5, as recited in claim 1, can easily be made by the skilled artisan by following the directions provided in the specification. Claim 1, and dependent claims therefrom, are enabled by the specification. Nothing more is required.

Rejection of Claim 10 Under 35 U.S.C. § 112, First Paragraph

The Examiner notes that claim 10 does not meet the enablement requirement under 35 U.S.C. § 112, first paragraph, absent a deposit. The Examiner further notes that Applicant has satisfied the enablement requirement by deposit of the cell line producing MAb 12G5. The deposit was made with the American Type Culture Collection (Rockville, MD) on June 25, 1997 under Accession No. HB 12372, which Accession Number was provided in the Preliminary Amendment filed on December 16, 1997. Thus, the rejection of claim 10 under 35 U.S.C. § 112, first paragraph, for lack of enablement should be withdrawn if the Examiner has not already done so.

Rejection of Claims 1-2 and 4-8 Under 35 U.S.C. § 102 (a) or § 102 (b)

Claims 1-2 and 4-8 stand rejected under 35 U.S.C. § 102 (a) or § 102 (b) as being anticipated by Feng et al., 1996, Science 272:872-877 (hereinafter "Feng"), because, according to

the Examiner, the antibodies of Feng are the same as those of the present invention. The Examiner further notes that Applicant's previously submitted Declaration of the inventor of the present application, James A. Hoxie, under 37 C.F.R. § 1.131, asserting that Feng cannot anticipate the instant invention since the date of Applicant's invention precedes May 10, 1996, the date of publication of Feng, would overcome this rejection if the Declaration is amended to include a statement that the reduction to practice was in the U.S. or a NAFTA or WTO member country.

Accordingly, an amended Declaration of the inventor, James A. Hoxie, under 37 C.F.R. 1.131, is enclosed herewith stating that Applicant's invention precedes the publication of Feng on May 10, 1996, and that the invention was reduced to practice in the U.S. before the date of publication of Feng. Therefore, and the Examiner's rejection of claims 1-2 and 4-8 under 35 U.S.C. § 102(a) or (b) should be withdrawn.

Rejection of Claims 9 and 10 Under 35 U.S.C. § 103 (a)

Claims 9 and 10 stand rejected under 35 U.S.C. § 103 (a) as being obvious under Feng, *supra*, because, according to the Examiner, the antibodies of Feng are the same as those of the present application, and the previously submitted Declaration under 37 C.F.R. §1.131 of the inventor of the present invention, James A. Hoxie, would overcome this rejection if it included that the work was performed in the U.S. or in a NAFTA or WTO member country.

Accordingly, as stated previously herein, the amended Declaration of inventor, James A. Hoxie, under 37 C.F.R. §1.131, enclosed herewith, stating that his invention precedes the publication of Feng on May 10, 1996, and that the invention was reduced to practice in the U.S. before the date of publication of Feng. Therefore, the rejection of claims 9 and 10 as being obvious over Feng under 35 U.S.C. § 102 (a) or (b) should be reconsidered and withdrawn.

Additionally, in light of the Declaration of inventor, James A. Hoxie, under 37 C.F.R. §1.131, enclosed herewith, the fact that Cohen (1996, Science 272:809-810) (hereinafter "Cohen"), which was published simultaneously with Feng on May 10, 1996, may, according to the Examiner in the previous Office Action (Paper No.11), suggest that Feng first disclosed fusin (now known as CXCR4) as a HIV cofactor, is not pertinent to Applicant's claims since Applicant has presented evidence that he was first to discover the claimed antibody. Thus, for the reasons

previously set forth herein with regard to Feng, Cohen cannot be prior art to the present invention since Applicant's invention also precedes Cohen. See Declaration of Hoxie pursuant to 37 C.F.R. § 1.131, enclosed herewith.

For the above-stated reasons, Cohen should not be considered pertinent prior art to Applicant's disclosure and the statement made by the Examiner to this effect in the previous Office Action (Paper No. 11, paragraph 10, at page 6) should be withdrawn and the rejection of claims 9 and 10 as being obvious over Feng should be reconsidered and withdrawn.

Conclusion

Applicant respectfully submits that each rejection of the Examiner to the claims of the present application has been either overcome or is now inapplicable, and that each of claims 1-2 and 4-10 is in condition for allowance. Reconsideration and allowance of each of these claims are respectfully requested at the earliest possible date.

Respectfully submitted,

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(Date)

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enc. Declaration of James A. Hoxie under 37 C.F.R. § 1.131